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Absorption and Distribution of Xenobiotics

by Frank G. Standaert*†

Extrapolation of pharmacokinetic data between species has been simplified by the advent of more sensitive methods of analysis of chemicals in body tissues and by the capability of inexpensive computers to perform complex calculations. These new methods enable investigators to observe the rates at which target tissues reach equilibrium in different species and to develop mathematical models of these processes. The evaluation of physiological pharmacokinetics from classical or compartmental kinetics is improving the ability to project the long-term behavior of chemicals in body fluids and organs based on independently derived physical, chemical, and physiological constants obtained from simple chemical reactions, tissue culture experiments, or short-term animal studies. Accurate prediction of chemical behavior by such models gives support to hypothetical mechanisms of distribution and accumulation, while significant deviations from predicted behavior signal the existence of previously unsuspected pathways. These techniques permit the simulation of the impact of linear, nonlinear, and saturation kinetics on chemical behavior; the prediction of integrated tissue exposure; and the mapping of the sequence of alternate metabolic pathways that lead to toxicity or detoxification. The discussion will identify the research needs for improving extrapolations between species.

Introduction

Conventional long-term, high-dose *in vivo* assays have a simple rationale: If there is something noxious about a chemical, then repeatedly giving maximum doses will make the noxious effect appear among a small group of test animals. Perhaps such thinking is adequate to address the qualitative question of whether a compound is noxious, but it has the serious drawback of not addressing the quantitative question of how much of the compound is needed to bring forth the noxious effect. Assays that use only two doses [i.e., the maximal tolerated dose (MTD) and one other] do not provide the experimental insight into the shape and slope of the dose-response curve that makes it possible to extrapolate from a high dose to a low dose. The problem is even more perplexing when the task is to extrapolate quantitatively across both dosage regimens and species, i.e., high doses in animals to low doses in human beings.

Frequently the extrapolation is made by the simple process of assuming that the same number of milligrams/kilograms/lifetime will produce equivalent results in animals and human beings. In reality, this extrapolation cannot be done unless there are species equivalence in responses and linear and/or known relationships between the magnitude of the dose administered and the magnitude (or frequency) of the response elicited.

Several papers in this symposium address the matter of whether there is a common mechanism of carcinogenicity among species. This paper will address some of the issues related to extrapolation from high doses to low doses. When the shape of the dose-response curve is not known, the problems of extrapolating between doses become very difficult (*1–3*). Under these circumstances, the relationship between the dose of a chemical administered to an animal and the concentration of that chemical at its site of action becomes the focus of study.

The dose-response curve is traditionally used for predicting the relationship between the administered dose and the response; however, the fact that the concentration of the chemical at its site of action and/or the time for which that concentration is maintained is more relevant than the dose that was administered is frequently overlooked. This discussion will focus on some of the factors that influence the relationship between the dose administered and the concentration reached and maintained at the site of action.

With the understanding that current knowledge of various aspects of dose extrapolation is deficient, a system will be reviewed by which extrapolation from one species to another and one dose to another may be attempted. However, it should be appreciated from the outset that this form of extrapolation is in its infancy and that many of the needed data or extrapolation parameters are not available at this time. While the limitations of knowledge cause large error factors to enter the calculations, even currently available information can produce results that are more accurate and more scientific than other systems currently used. The estimates will improve as knowledge of the basic biological processes governing carcinogenicity and pharmacokinetics becomes available.

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*Department of Pharmacology, Georgetown University, Schools of Medicine and Dentistry, 3900 Reservoir Road, N.W., Washington, DC 20057.

†Current address: Medical College of Ohio, 3000 Arlington Avenue, Toledo, OH 43699.

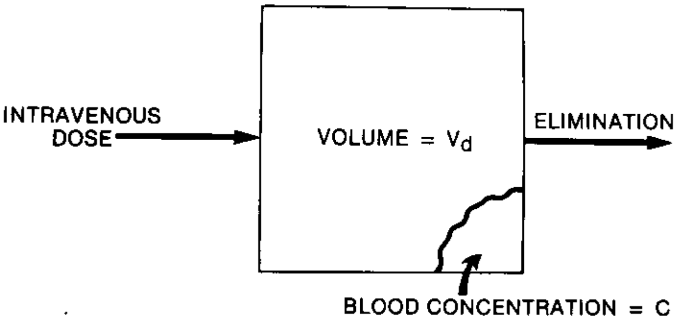

FIGURE 1. Determinants of concentration. Modified from Greenblatt and Shader (*17*).

Extrapolation When Pharmacokinetic Factors Are Linear

To make the extrapolation from administered dose to the concentration *in vivo,* it is necessary to consider the absorption, distribution, and elimination of the compound at the doses administered to the species in question. Concentration is defined as quantity/volume (Fig. 1). For *in vivo* studies, the quantity of the chemical in the body is the difference between the amount absorbed and the amount eliminated. Because the chemical is eliminated continuously, the concentration may vary widely if the chemical is given in pulses (e.g., in a single daily dose). A better understanding of the instantaneous value of the concentration may be determined by considering the rate of absorption and the rate of elimination.

Volume is directly related to animal size. In pharmacokinetic studies, it is important to understand that the volume of the study animal provides information about the amount of potential solvents (e.g., water, lipid, protein) that is available in the animal's body to concentrate xenobiotics and the manner in which the chemistry of a particular xenobiotic will dictate partition among those solvents (*4*).

For orally administered xenobiotics, there are many factors that may influence the absorption and the behavior of a particular compound at a specific time (*5–11*). These include anatomy, age, and pK_a of the compound, pH of the gut, diet, and gut flora. There are two major factors that dominate the consideration of xenobiotics absorption in study animals (*12–16*). First, nearly all xenobiotics cross the GI tract from the gut lumen to the blood by simple diffusion. The rate of diffusion is controlled by the concentration gradient across the GI wall. Second, the major barrier to diffusion is the GI wall. The wall behaves as if it were a sheet of lipid separating water phases on one side (i.e., the GI lumen) from those on the other (i.e., the blood). It follows that in order to be absorbed predictably, a xenobiotic must be water soluble to be dissolved in the GI lumen and be carried away by the blood and lipid soluble so it can diffuse across the GI wall.

Many compounds do not have the blend of lipid and water solubilities to enable their efficient absorption. However, those xenobiotics that demonstrate these unique qualities may be presumed to be absorbable by all species, unless the experiment is modified by such external factors as the vehicle used, diet, debilitation, diarrhea, or bacterial degradation. These modifications can be understood before the experiment or observed during study to permit appropriate corrections by the investigator. Once the xenobiotic crosses the gut wall, it enters the gastrointestinal tissues and then the portal vein. From there it courses through the liver and into the systemic circulation (Fig. 2). The xenobiotic is distributed by the blood to all tissues, including the target tissue containing the site of action.

If there is no species-specific or rate-limiting process involved in the absorption of the xenobiotic into the blood and passage through the presystemic circulation

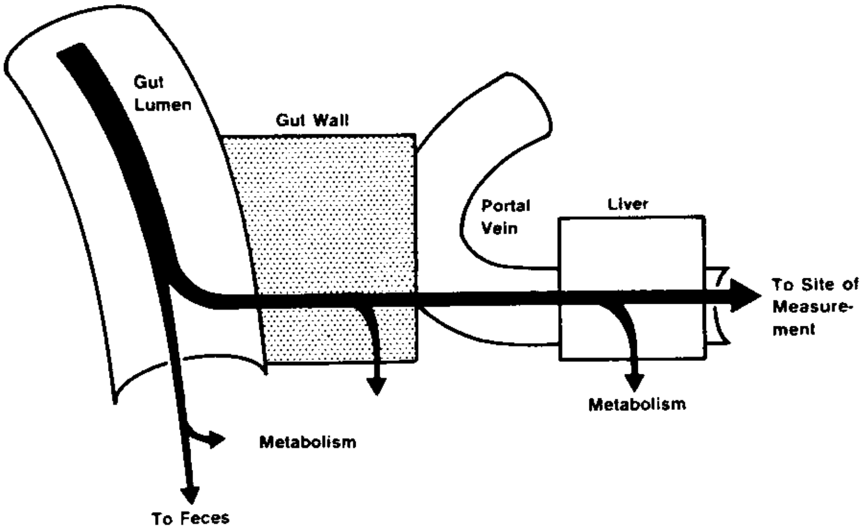

FIGURE 2. Pathways followed by xenobiotics administered orally. Modified from Gibaldi (*13*).

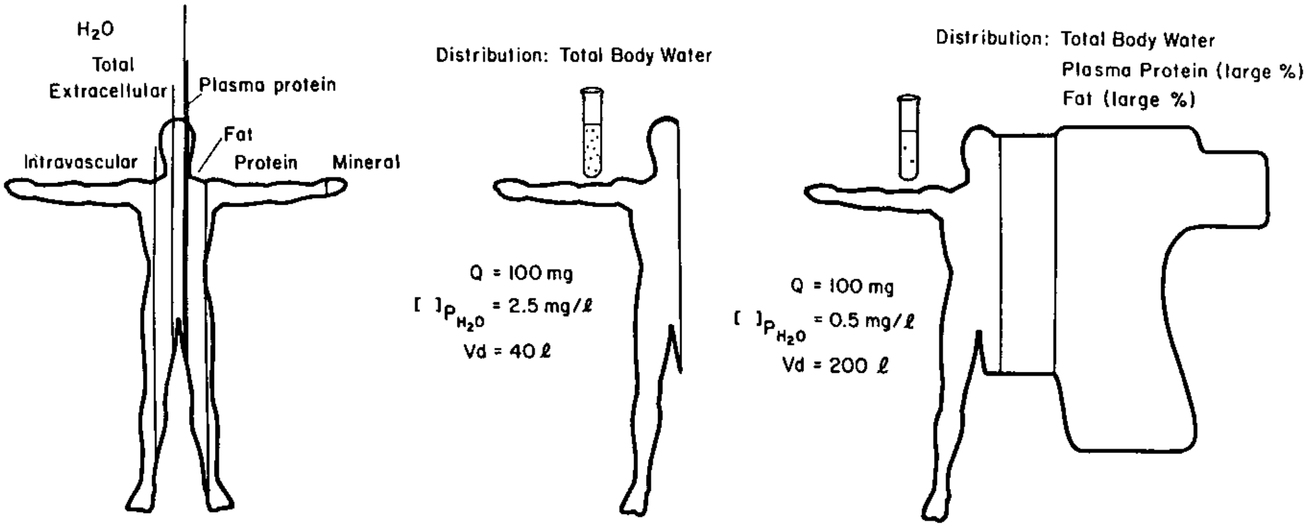

FIGURE 3. Illustration of the affect on apparent volume of distribution of solubility in body constituents. Left: the major chemical constituents in the body; center: apparent volume of distribution of compounds soluble only in water; right: apparent volume distribution of compounds soluble in water, fat, and protein. Q; quantity of xenobiotic administered IV; [$]P_{H_2O}$ concentration of xenobiotic in plasma water at equilibrium; v_d, apparent volume of distribution.

(i.e., gastrointestinal tissues, portal blood, and liver), the agent is distributed to and among the organs. The rate of distribution and the ultimate concentration of the chemical in the organs vary between species, but the factors governing these parameters are understood and can provide a means for extrapolating from one species to another.

The use of pharmacokinetic methods to extrapolate between species is based upon knowledge of the rate at which the chemical is delivered to the various tissues and the ultimate concentration attained in each of the various tissues. The rate at which a chemical is delivered to an organ depends upon the rate at which the blood containing the chemical is delivered to the organ. Information on the rate of blood flow to organs of laboratory animals is available in the literature (*18–23*). The rate of delivery of a chemical to any particular organ can be predicted from information on the rate of blood flow. Similarly, in the absence of destruction of the compound in the organ (i.e., metabolism), the compound is removed by blood, and so the rate of elimination may also be calculated.

When the rate of delivery and the rate of elimination are in balance, the system is in equilibrium, and the quantity of the chemical in an organ is purely a function of the solubility of the chemical in the solvents in that organ. This is referred to as a partitioning of the chemical among the various potential solvents and can be estimated from data obtained *in vitro* (*4,16*).

The preferential concentration of a chemical in one tissue rather than another leads to an apparent variation in the volume of distribution of chemicals, and so can affect the calculation of concentration (*24,25*). For example, if the concentration of the chemical in blood water is to be calculated, it will not be dependent upon the real volume or size of the animal, but it will be dependent on the apparent volume in which the chemical is distributed (i.e., the volume of the available water-soluble partition). The apparent volume will be much smaller for a chemical that is highly soluble in water and poorly soluble in lipid than for a chemical that has the opposite set of characteristics (Fig. 3). Since the apparent volume of the water-soluble chemical is smaller than that of the lipid-soluble chemical, the concentration in water will be much greater for the former than for the latter, even if the same amounts of these two chemicals enter the body.

The rate of delivery, the rate of elimination, and the apparent volume of the solvent partition can be determined for any particular chemical given to a laboratory animal. Furthermore, procedures are available for extrapolating the values from one species to another using mathematical methods of scaling between species. The characteristics of available mathematical methods for scaling have been discussed by several investigators (*18,19,21,26–30*). Allometry is among the more widely used procedures currently used for scaling dose between species. This procedure evaluates the way in which various physiologic parameters are related to the weight of the animal according to the general formula $y = aW^b$ in which y is the value of the parameter in one species, W is the weight of the species, and a and b are empirically determined interspecies scaling factors. By taking the logarithm of both sides, this equation may be rearranged to $\log y = \log a + b \log W$.

This approach permits estimation of important anatomic or physiologic parameters that affect chemical absorption, distribution, or clearance (*31,32*). By appropriate use of these factors, corrections may also be made for differences in the lifetimes of the animals and estimates of various rate functions may be derived (*18,19,26,29*).

Scaling measures allow normalization of various parameters among species, but deal with the parameters on an item-by-item basis (e.g., volume of distribution, liver weight, time) and are not by themselves capable of providing a model of a whole body or of the dynamic status of a xenobiotic (Figs. 4–7). This approach can be combined with modeling via physiological pharmacokinetics to provide a better picture of scaling (*23,33–35*).

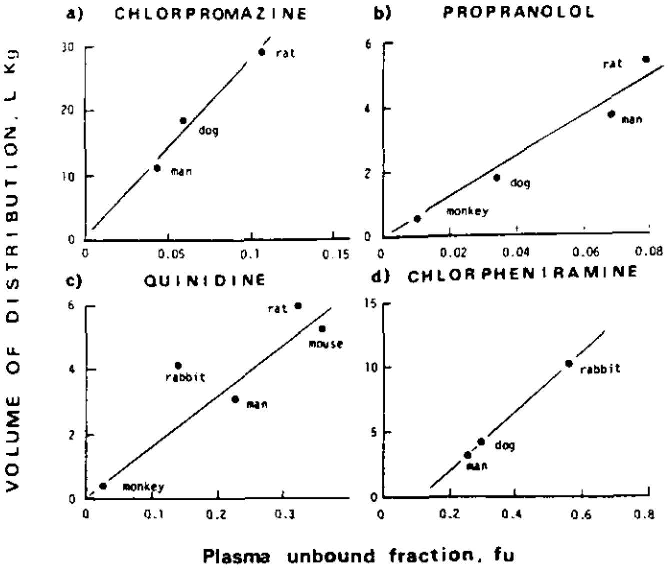

FIGURE 4. Apparent volume of distribution of four xenobiotics when appropriate scaling factors are used (*29*).

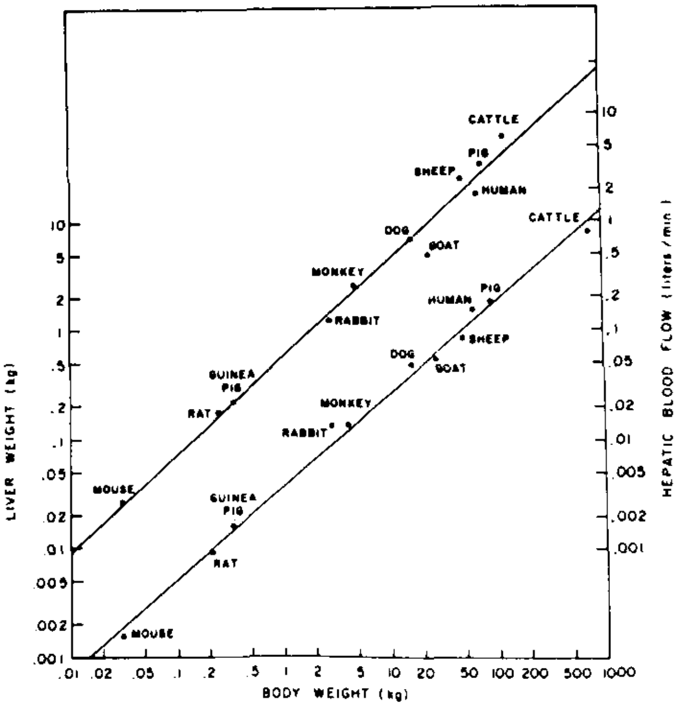

FIGURE 5. Liver weight (left scale and upper line) and hepatic blood flow (right scale and lower line) as a function of body weight in various species. Modified from Boxenbaum (*26*).

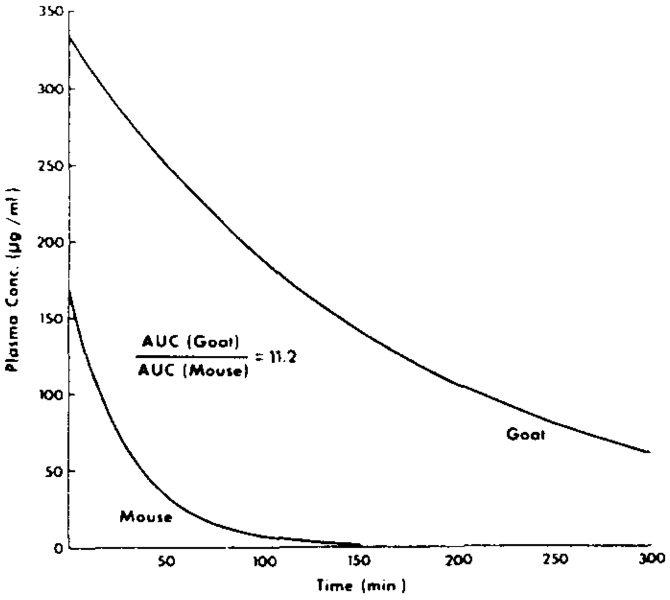

FIGURE 6. Relationship of plasma concentration as a function of time in two species, uncorrected. AUC, area under curve. Modified from Boxenbaum (*18*).

Physiological pharmacokinetic models differ from the more familiar compartmental pharmacokinetic models in that they are constructed from an array of known physiological and chemical parameters that enable prediction of chemical behavior prior to the experiment. In contrast, compartmental kinetics begin with experimental data and seek to construct a mathematical model of the body that fits the observed data. Physiological models become increasingly accurate as additional physiological factors are incorporated into the model. However, with the addition of each physiological component, the mathematics become increasingly complex and computers are needed to solve the numerous differential equations. An example of a physiologic model for use in pharmacokinetics is shown in Figure 6. The application of an interspecies scaling factor to each parameter adds to the mathematical complexity, but allows the model to be extrapolated from one species to another. An example of the data used for interspecies scaling of the physiological model of Figure 8 is presented in Table 1.

Interspecies extrapolation by this method is a recently developed approach that is still evolving. The approach has several limitations. For example, the information presented in Figure 5 is plotted on a log-log scale to make the scattered deviation of data around these lines appear smaller than it would in a nonlog scale plot of this information. Nonetheless, the method has been used to predict the pharmacokinetic behavior of several drugs (*23,31,36,37*). This approach could be adapted to estimate the dose extrapolations involved in carcinogenicity assays.

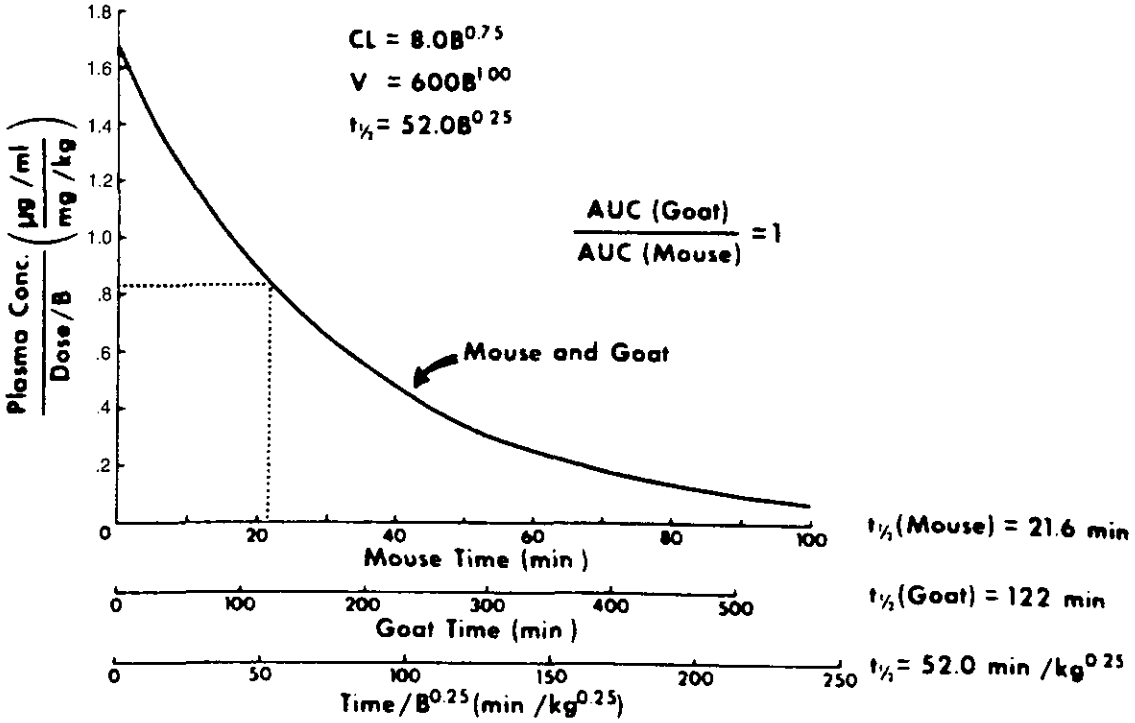

FIGURE 7. Relationship of plasma concentration as a function of time in two species, corrected by factors that accommodate for differences in life span of the two species. Line at bottom contains general scaling factors that may be used to approximately normalize time scales among species. Cl, clearance; V, volume; AUC, area under curve; B, body mass, kilograms. Modified from Boxenbaum (*18*).

Table 1. Physiological parameters for modeling in the 0.25-kg rat and the 70-kg man.[a]

	Volume, mL		Blood flow rate, mL/min	
Compartment	Rat	Human	Rat	Human
Brain	1.2	1,500	1.1	760
Lung	1.2	1,200	44.5	6,330
Heart	1.0	300	4.2	240
Liver	11.0	1,500	14.7	1,580
Kidney	2.0	300	11.4	1,240
GI tract	11.1	2,400	12.0	1,200
Muscle	125.0	30,000	6.8	300
Skin	43.8	7,800	4.5	1,950
Adipose tissue	10.0	12,200	1.8	260
Blood				
Artery	6.8	1,800		
Vein	13.6	3,600		

[a] Modified from Igari et al. (*23*).

Extrapolation When Pharmacokinetic Factors Are Nonlinear

Extrapolation by the approach described is based on a premise that does not apply to the usual carcinogenicity assay conditions. This is because many of the kinetic parameters used in the model are not known, and these parameters cannot always be normalized across doses or species using mathematical methods. One reason that the proposed method cannot be currently applied is that the extrapolation procedures presuppose that changes in chemical concentration follow first-order kinetics in all species and at all concentrations (i.e., that the fraction of chemical absorbed or eliminated per unit time is constant and independent of concentration). If this condition is not met, then the pharmacologic phenomena being scaled are not linear and it is usually not possible to predict from knowledge of one circumstance what is likely to happen at another. The analytic approach requires that most processes, particularly the elimination processes, follow first-order kinetics. Carcinogenicity assays, however, are conducted with very high doses of the xenobiotic that almost certainly saturate the eliminating process so that clearance follows zero-order kinetics. If this latter case prevails, then it may not be possible to extrapolate from knowledge of the dose administered to the item that must be known (i.e., the concentration of the chemical at its site of action).

Zero-order kinetics describe a process in which the elimination of a compound occurs at a constant rate, regardless of concentration. This is expressed mathematically by the equation $-dc/dt = k$. First-order kinetics describes a process in which the elimination of a compound is proportional to the concentration, $-dc/dt = kc$ (*12,13,17,38–40*). The differences in the processes are shown graphically in Figure 9.

This difference is seen in organs of elimination (e.g.,

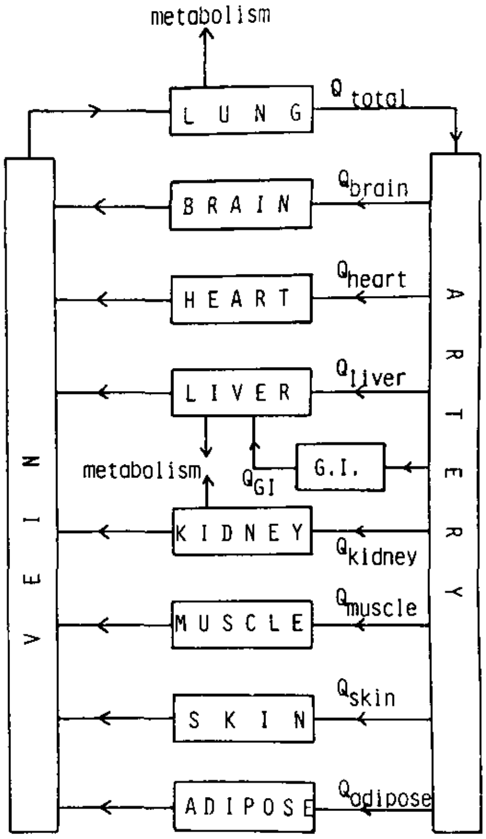

FIGURE 8. Diagram of a physiologically based pharmacokinetic model used to predict drug distribution. Organs are represented as compartments perfused by the vascular system. Q, quantity of chemical. Modified from Igari et al. (*23*).

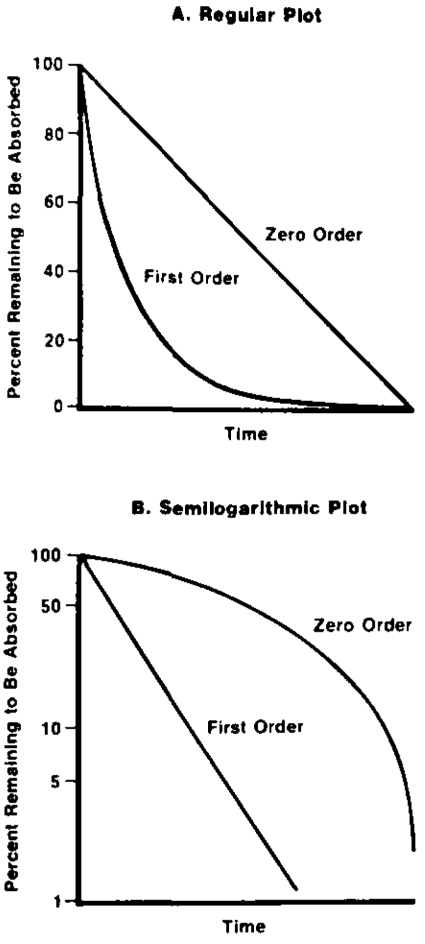

FIGURE 9. Zero-order and first-order elimination kinetics plotted on arithmetic (*A*) and semilogarithmic (*B*) scales (*40*).

liver). All chemicals entering the body via the GI tract must go through the presystemic circulation (*38*) where they are subject to destruction by enzymes in the intestine and/or liver (Fig. 2). This destruction is an active, enzyme-mediated process, which, although very efficient, can also be limited in capacity and may be easily overloaded. The enzymes are limited in both the rate at which individual molecules can catalyze a reaction and in the number of enzyme molecules present in the tissue. As a result, the liver may metabolize only a specific number of molecules per second. If additional molecules of xenobiotic are present in the portal blood, they pass through a system in which the destructive processes are fully saturated, thereby gaining entry to other compartments of the body unchanged.

The basic characteristics of an enzyme system are specified in the Michaelis-Menten formula, which can be expressed mathematically as follows:

$$V = V_{\max} \cdot C/K_{\mathrm{m}} + C$$

This relationship requires that V (the velocity with which a xenobiotic is metabolized) increases linearly only when C (the concentration of the substrate for the enzyme) is very small compared to the capacity of the enzymatic system. As C increases, velocity increases as a nonlinear function until the reaction becomes saturated and V becomes a constant that does not change with further increases in C (*6,13,39*). A graphic representation of the relationship between V and C is shown in Figure 10.

This relationship between rate of metabolism and enzyme substrate concentration is important because it explains that the whole system changes when the concentration of the xenobiotic is sufficient to saturate the elimination enzymes. Under these conditions the kinetics of the changed system become complex, and there is no easy way of predicting what will happen to the compound or to the test animal (*6,41,42*).

For example, the xenobiotic may accumulate in the organism without limit when the elimination mechanism is saturated. Without a means for the organism to eliminate the excess material, it stays in the body, increasing in concentration with each additional dose (Fig. 11). The chemical may have toxic effects not seen at lower concentrations because the concentration may rise to extraordinary levels.

A variety of nonspecific effects may be caused by the amount of chemical in the body. If nothing stops the

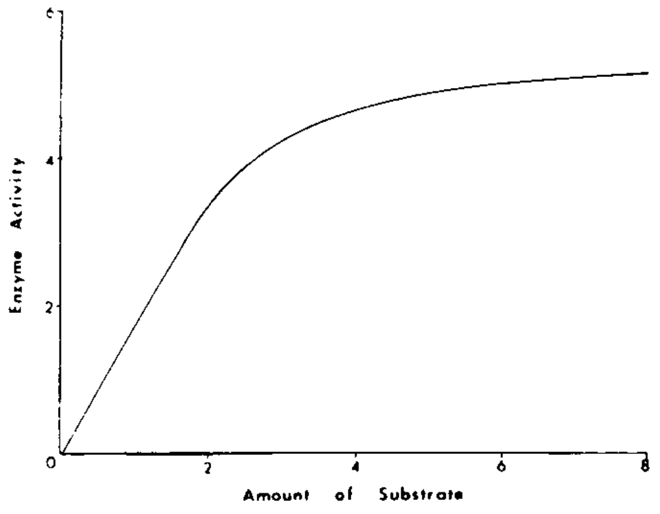

FIGURE 10. Relationship between the velocity of reaction and the concentration of substrate expected of a compound subject to Michaelis-Menten enzyme kinetics.

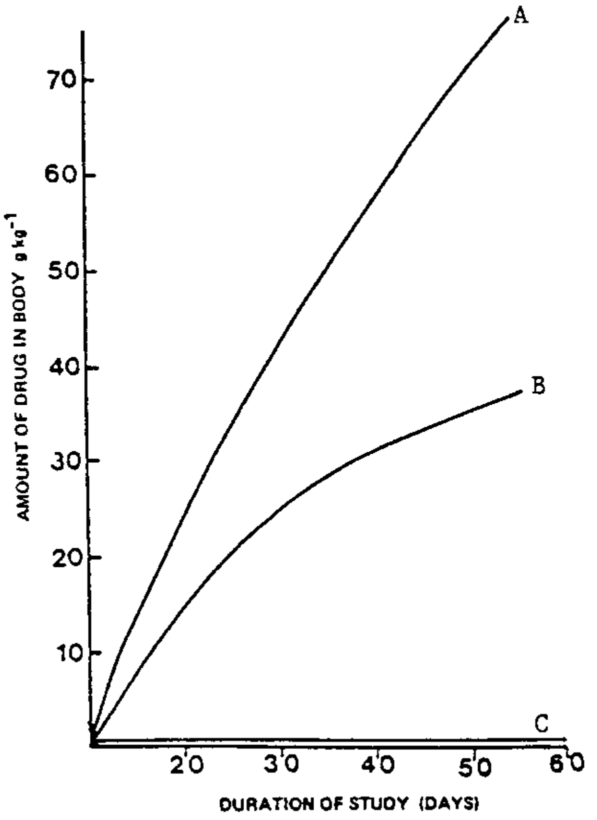

FIGURE 11. Effect on concentration of material in the body when the rate of absorption is less than, approximately equal to, and greater than V_{max} of the eliminating enzymes. Lines *A*, *B*, and *C*: compound administered at rate of 1500, 1000, and 100 mg/kg/day, respectively. V_{max} is 1100 mg/kg/day (*6*).

rise in concentration, the animal will die; however, sometimes secondary metabolic pathways are invoked at the high concentration. These may limit the increased body burden of chemical, but they may also initiate new mechanisms of toxicity, particularly if a metabolite is toxic (*3*).

Saturation of metabolizing enzymes can have different effects on toxicity, depending upon whether the parent molecule or its metabolite is the toxic agent (Fig. 12). If toxicity is due to the parent molecule, toxicity can increase as concentration rises, because more parent molecules escape destruction and become available systemically as the metabolizing enzymes are saturated. On the other hand, if toxicity is due only to a metabolite, then toxicity reaches a plateau and will not increase with dose after a saturating concentration is attained, because the organism cannot increase the amount of metabolite it makes regardless of how much chemical becomes available.

Saturation of elimination pathways can bring forth toxicity not usually seen. For example, this can occur if the compound is usually destroyed before it leaves the liver. In this case, saturation of liver enzymes will cause some of the parent molecules to spill into the systemic circulation and initiate effects that would not be seen in more moderate circumstances (Fig. 13). In this situation a major difference in toxicity may be observed in animals given a xenobiotic by gavage and those given an identical dose in the water or diet. Administration of the chemical by gavage delivers a high pulselike concentration in the portal blood that may exceed the concentration needed to saturate liver enzymes. In this case, the parent chemical will spill into the systemic circulation. A chemical administered in the

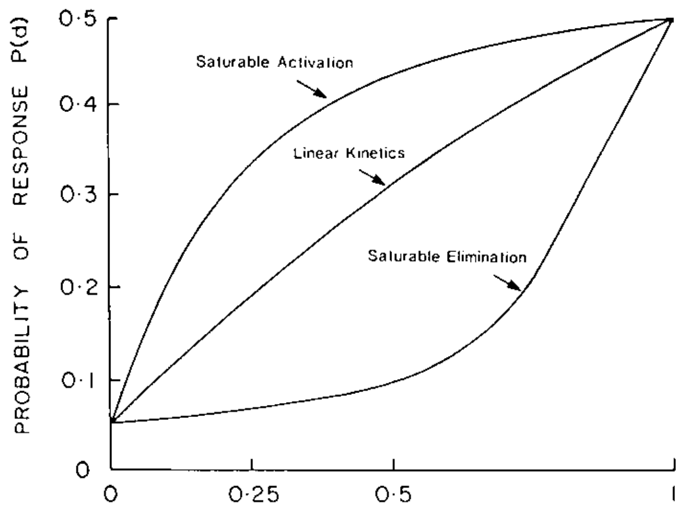

FIGURE 12. Relationships between administered dose and toxic material in body. Center line depicts situation in which parent molecule is the toxic material and clearance is not saturated. Upper line depicts situation in which the toxic agent is a metabolite of the parent molecule and the enzymes are saturable. Bottom line depicts situation in which the parent molecule is the toxic material and the clearing enzymes are saturable (*3*).

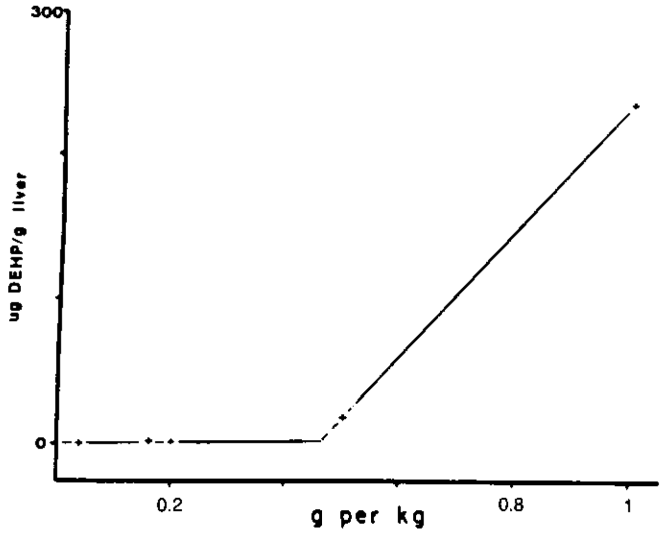

FIGURE 13. Relationship between administered dose and amount of toxic material in systemic circulation in a situation in which small doses of orally administered material are cleared by the liver but larger doses saturate the clearing process (*44*).

diet, however, tends to be ingested over a period of many hours (*43*), and the resulting concentration in the portal blood may never reach enzyme saturation levels.

Summary

On the theoretical basis described in this presentation and elsewhere, it is easy to understand why there is so much concern about the scientific accuracy with which we extrapolate from animal carcinogenicity assays to the human situation. The base of knowledge necessary to make the extrapolation is currently incomplete. This is because on a qualitative basis, there is uncertainty about the mechanisms of carcinogenesis, and on a quantitative basis, there are inadequate data to extrapolate from dose to dose.

For the long term, there is a need to continue study of the mechanisms of carcinogenesis. In the context of this presentation, the most important factors that must be known are the relationship between the concentration of the agent at its site of action and the response of the biologic system to that concentration. There is also a need to know the shape of the dose-response curve for the carcinogenic agent and whether the carcinogenic agent is the parent molecule or one or more of its metabolites. Until these facts are known, the ability to extrapolate knowledgeably from test situations in laboratory animals to humans will be limited because there is no understanding of what is being extrapolated to where.

While awaiting the results of the studies that will provide the needed knowledge, present methods can be improved by applying available information about carcinogenesis and pharmacokinetics. There is a need to expand quantitative research programs. Preliminary studies of compounds to be tested in chronic assays can be enhanced to permit a better understanding about physiochemical processes and to enable prediction of distribution patterns. Absorption can also be studied under the conditions of the assay, or if necessary, the assay can be redesigned to take account of absorption. The metabolism of the agent can be studied to determine whether or not the clearing processes will become saturated by the proposed doses of the agent and what this will mean in the interpretation of the assay results.

Much of this needed information can be provided by existing technology. For example, sampling of blood will provide information about the pharmacokinetics of absorption, clearance, and accumulation of the chemical. The study of a wider range of doses than current practice could give information about the shape of the dose-response curve and may indicate whether or not an active metabolite is involved in the toxicity. Consideration of the known physiological and biochemical differences among species will improve understanding of interspecies projections.

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